EXHIBIT 20

Comments of the Biotechnology Industry Organization
Re: Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation.

April 18, 2001

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The Biotechnology Industry Organization (BIO) is pleased to submit comments to the Food and Drug Administration (FDA) on the proposed rule "Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation." 66 Fed. Reg. 4688 (January 18, 2001) (the Proposed Rule or FDA's Proposal)./

I.INTRODUCTION

BIO is the largest trade organization to serve and represent the biotechnology industry in the United States (U.S.) and around the globe. BIO represents more than 950 biotechnology companies and academic institutions engaged in biotechnology research, which includes research and development of health care, agricultural and environmental biotechnology products, as well as industrial biotechnology applications. The amount of money invested in the U.S. biotechnology industry exceeds 97 billion, much of which is focused on smaller companies./

Companies willing to undertake the time and expense associated with the development of gene therapy and xenotransplantation products represent a minority of the biotechnology industry. Of the 546 BIO members that are classified as biotechnology companies, approximately 10% are involved in gene therapy research and approximately 13% in xenotransplantation research. Of these companies, most operate solely at the research and development level with regard to gene therapy and xenotransplantation products. The first biologics license application (BLA) for a gene therapy product may soon be submitted to FDA. Researchers continue to explore different indications, routes of administration, sources of therapeutic materials, dosing regimes, patient populations, combination therapies, and novel vectors.

Biotechnology companies in pursuit of commercially viable gene therapy and xenotransplantation products do so at enormous entrepreneurial risk. They rely on the promise of future revenues to support the heavy investment required for the research, development, and clinical investigation. Smaller companies, especially, must rely on private venture capital and are particularly sensitive to any event that may undercut their efforts in what is a highly competitive field both scientifically and financially.

II. EXECUTIVE SUMMARY

Under the Proposed Rule, FDA would now require public disclosure of what both industry and FDA considered for 60 years to be confidential commercial or trade secret information in a gene therapy or xenotransplantation Investigational New Drug exemption application (IND), including any amendment and annual report thereto. Current FDA regulations and the United States Code prohibit the release of such information. Under the Proposed Rule, however, such information would be made available to the public, at virtually the same time it is submitted to the agency. While FDA's Proposal identifies several limited exceptions to the release of information, by the agency's own estimation "the vast majority" of information in an IND would be publicly disclosable.

The notion that FDA should release investigational information in this manner fundamentally reverses long-standing FDA policy; no other therapeutic products under FDA's jurisdiction are subject to such disclosure requirements during their development. To the contrary, for at least the past 60 years, FDA, the Department of Justice, and the federal courts have treated the information submitted as part of an IND as confidential commercial and trade secret information, unless specifically made public by the manufacturer of the product. FDA has stated that its change in policy with regard to the release of this

information for gene therapy and xenotransplantation products is necessary because these products pose unique public health issues requiring public education and input.

FDA's Proposal is fatally defective as a matter of fact, law and public health policy. Among the factual, legal and policy reasons supporting BIO's view, are the following:

- FDA's assertion that the information they wish to make public is "no longer confidential" is incorrect. FDA has made overbroad generalizations as to what information currently is made public by companies developing these products. Much of the information identified by FDA as no longer confidential is *not* in the public domain and continues to meet the judicially-imposed definition of confidential commercial and trade secret information. The release of such information is protected against disclosure under Exemption 4 of FOIA, where disclosure would result in substantial competitive harm. FDA has not established a factual basis for reversing at least 60 years of FDA, Department of Justice, and judicial decisions regarding the confidential nature of such information.

- Gene therapy and xenotransplantation companies have willingly cooperated with FDA, HHS and NIH to provide the information and scientific expertise necessary to allow public dialogue on an array of public health issues. BIO anticipates that such cooperation will continue in the future, even without the mandatory disclosure of information required under the Proposed Rule. Historical cooperation by industry should not now be used by the government to conclude that most IND-specific information is no longer confidential.

- To the extent specific safety concerns about an investigational product arise, FDA has a long and substantial record of utilizing its regulatory authority to prevent or stop such clinical investigations until the safety issues are resolved. Thus, the Proposed Rule will not substantially further FDA's claimed goal of improving patient safety.

- As the companies and the product categories mature, the consequences to the industry of releasing confidential and trade secret information will become more significant. Retaining the confidential nature of such information will become increasingly important because improper disclosure will certainly cause substantial competitive harm. FDA is unjustified in treating the investigational information for gene therapy and xenotransplantation products differently than it does such information from the rest of the pharmaceutical and biotechnology industry.

- Companies have the right to have any proposed release of their confidential commercial information evaluated on a case-by-case basis. The fact that some data has historically been released by individual companies is not dispositive, nor should companies be penalized in the future for such cooperation.

- Disclosure of IND information in the categorical fashion mandated by FDA's Proposal violates the notice requirements of Executive Order 12,600. FDA's Proposal re-defines certain information as no longer confidential. By doing so, FDA seeks to deny companies of the right to contest in court, pursuant to FOIA and the Administrative Procedure Act,

FDA's decision to release specific information that a company has kept confidential and whose release would cause substantial competitive harm.

- FDA's Proposal requires the public release of information that consists of manufacturing methods or processes. Such information constitutes trade secret information and it would be a criminal violation of section 301(j) of the Federal Food, Drug, and Cosmetic Act to release such information. FDA has no discretion to authorize the release of such information.

- Public disclosure by FDA of the information identified in the Proposed Rule violates the Trade Secrets Act, which makes it a criminal offense for an FDA employee to release trade secret or confidential commercial information unless "authorized by law." The Proposed Rule and the statutory provisions cited by FDA as the basis for the regulation do not provide the necessary legal authority to support release of the information under that provision.

- FDA's explanation of why it has decided to adopt a blanket disclosure rule at this time, for this class of products, is inadequate as a matter of law. FDA has failed to establish a necessary link between the specific risks it is seeking to address (*e.g.*, the risk of communicable disease) and the proposed solution. Moreover, FDA fails to show that it considered other alternatives—including less disruptive and more narrowly focused solutions.

- Public disclosure by FDA of the information identified in the Proposed Rule violates the Takings Clause of the Fifth Amendment to the Constitution of the United States.

- Section 505(i) of the Food, Drug and Cosmetic Act does not provide the legal basis to place a manufacturer's IND on clinical hold if the manufacturer does not comply with FDA's Proposal.

- If the "vast majority" of data in an IND is made available to the public on an immediate basis, it will have a material impact on capital development; it will seriously disrupt a company's disclosure obligations under SEC requirements; it will put competitor companies on an almost equal footing with the company developing the product, thereby disrupting the normal product development process; it will provide potentially misleading information to the public, patients, and consumers; and, it will place an enormous administrative and economic burden on both the company and FDA.

BIO and its member companies appreciate the value of maintaining a public dialogue on the health and safety issues that will arise as the development of gene therapy and xenotransplantation products proceed. BIO believes, however, that the public health will best be served by ensuring that information that forms the basis of that dialogue is relevant, accurate, and timely. Thus, in filing these comments BIO does not intend to suggest any decrease in industry's strong commitment to working with FDA to ensure that the interests of patient safety and public health remain paramount. Nor is industry any less willing, under appropriate circumstances, to cooperate with FDA in the voluntary release of investigational product information. Rather, BIO objects to the mandatory disclosure of valuable confidential commercial and trade secret information that would become standard practice under the Proposed Rule and would

subject companies to significant competitive disadvantage, in many cases without any corresponding benefit to the public health or safety.

III. BACKGROUND

A. Gene Therapy

Gene therapy is a promising technology that uses genes themselves as therapeutic agents to treat hereditary genetic disorders. FDA defines human gene therapy as "the administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use." In gene therapy, a faulty or missing gene can be replaced to offset a genetic cause of a disease. Sometimes in gene therapy, cells are removed from a patient, altered to counter the genetic cause of the disease, and put back into the body. Sometimes new cells are introduced to produce needed cell-growth factor or perform a beneficial cellular function.

Recent reports indicate that the hope for gene therapy is well placed. For example, several gene therapy products for the treatment of cancer have demonstrated safety, and have begun to demonstrate efficacy in clinical trials./ In addition, researchers in France recently reported that infants suffering from Severe Combined Immunodeficiency Disease (SCID) have had their immune systems restored by gene therapy./ And last year, American researchers described preliminary data that could lead to a gene-based cure for the debilitating blood disease, hemophilia./

Historically, individual gene therapy companies have cooperated with the NIH and provided certain limited information to the RAC. A limited review of industry submissions to NIH shows that companies provide gene therapy protocols; informed consent documents; and brief summaries of safety, efficacy and manufacturing information in response to the questions contained in the existing NIH Guidelines. In addition, the companies provide safety reports and annual reports as well. Not all gene therapy protocols and related information, however, are provided to the RAC. Clinical trials may proceed—and, in fact, are proceeding—without NIH funding and at medical institutions that do not receive NIH support. There are also foreign studies currently underway. None of these types of clinical trials fall under NIH jurisdiction and therefore information on them is not necessarily disclosed to NIH. In short, some companies have the option of protecting all of their confidential commercial and trade secret information by proceeding outside the scope of NIH. FDA's Proposal, however, seeks to require disclosure even for those who have taken specific steps to protect their information.

B. Xenotransplantation

FDA defines xenotransplantation as ". . . any procedure that involves the transplantation, implantation, or infusion to a human recipient of either (a) live cells, tissues, or organs from a non-human animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live non-human animal cells, tissues or organs."/ Organ transplantation has been found to be an especially effective, cost-efficient treatment for severe, life-threatening heart, kidney, lung and other diseases. In some cases, it is the only effective treatment. Unfortunately, however, the waiting list for patients in the U.S. for organ transplants grows at a rate of over 20 percent per year. Each year, less than one-third of the people listed receive solid organ transplants, so that approximately 10 people die each day waiting for organs to become available.

The most significant obstacle to xenotransplantation is the human body's immune system. When tissue not recognized as human is introduced into the body, hyperacute rejection occurs the body cuts off the flow of blood to the donated organ. The most promising method for overcoming hyperacute rejection is believed to be genetic modification. By inserting human genetic material into pigs or other donor animals, it is believed that the human body will recognize the new organ as human and begin to use it as its own. Several biotechnology companies are working to overcome hyperacute rejection and other obstacles to xenotransplantation.

Unlike gene therapy, where individual companies have been providing a limited amount of information to the RAC for over a decade, there has been no such process for the public submission of information to the government by xenotransplantation companies. Rather, at various public meetings, individuals companies have made public presentations on various aspects of their product development activities. These presentations have been made at the request of public officials, with only certain companies voluntarily agreeing to participate.

C.FDA Regulatory Framework

Primary responsibility for the regulation of new medical products, including their clinical testing, rests with the Food and Drug Administration. FDA derives this authority from two statutes: the Federal Food, Drug, and Cosmetic Act (FD&C Act),/ which provides a basic framework for regulation of drugs and devices, and the Biologics Act of 1902,/ now codified as part of the Public Health Service Act,/ which gives federal officials authority over "biological products" including "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product."/

Gene therapy products (for instance, viral vectors containing genetic material to be transferred) and xenotransplantation products fall within the definition of biological products and are subject to the licensing provisions of the Public Health Service Act (as well as to some of the provisions such as the "investigational new drug" provisions of the FD&C Act). Thus, FDA is the federal agency charged by statute with regulating new products derived from recombinant DNA technology. FDA has stated unambiguously that "all gene therapy products are regulated by the FDA."/ More recently, FDA has made it clear that xenotransplantation products are also subject to FDA regulation under both the Public Health Service Act (42 U.S.C. § 262) and the FD&C Act. FDA further stated that "In accordance with the statutory provisions governing premarket development, xenotransplantation products are subject to FDA review and approval. Investigators of such products should obtain FDA review of preapproved xenotransplantation clinical trials before proceeding."/ Generally speaking, this requires an applicant for marketing approval to demonstrate, through carefully controlled clinical trials, that the product is safe and effective, or in the case of a biologic, safe, pure, and potent.

Any entity wishing to administer an investigational drug product (including a biologic) to humans must submit an investigational new drug application (IND) to FDA. FDA's primary objective when reviewing an IND is to assure the safety and the rights of research subjects./ When the investigation progresses to phases 2 and 3, FDA also reviews the IND to assure that the quality of the scientific evaluation is adequate to permit an evaluation of the product's effectiveness and safety./ To enable FDA to accomplish its objectives, sponsors must provide specific categories of information for FDA's review, prior to initiating the IND studies.

The central focus of a sponsor's initial IND submission should be on the general investigational plan and on the clinical protocol./ The general investigational plan provides a brief description of the overall plan for investigating the product for the following year and should include the rationale for the drug or the research study; the indication(s) being studied; the general approach for evaluating the drug; an estimate of the number of patients that will receive the experimental therapy; and any anticipated risks of particular severity or seriousness./ The clinical protocol will vary with respect to the level of detail depending on the phase of investigation. Regardless, clinical protocols included in the IND should, at a minimum, contain a statement of the study's objectives and purpose; patient inclusion and exclusion criteria; an estimate of the number of patients; a description of the study design including control groups and methods for minimizing bias; method for determining the dose(s); duration of individual patient exposure to the experimental therapy; the observations and measurements being made to accomplish the objectives of the study; and a description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug and minimize risk./

Although the initial IND focuses on the general investigational plan and the clinical protocol, FDA also requires the submission of information regarding the chemistry and manufacturing of the product as well as data from animal and previous human studies. The chemistry, manufacturing and control (CMC)

information must be submitted for both the active ingredient (drug substance) and the final therapeutic product, in addition to a description of the product labeling and an assessment of the potential environmental impact of manufacturing the product./ The CMC information regarding the active ingredient must describe its physical, chemical, or biological characteristics; state the name and address of its manufacturer; provide the general method of its preparation; include acceptable limits and analytical methods used to assure its identity, strength, quality, and purity; and present data supporting its stability./ CMC information regarding the final therapeutic product must include a list of all components used to manufacture it; describe its quantitative composition; state the name and address of its manufacturer; provide a brief general description of how it is manufactured and packaged; include acceptable limits and analytical methods used to assure its identity, strength, quality, and purity; and include information assuring its stability./

Data from previous animal and human studies must be adequate for the sponsor to conclude that administering the experimental therapy to research subjects will be reasonably safe. Such information must include sections describing the pharmacological effects and mechanism(s) of action of the drug in animals; information on the absorption, distribution, metabolism, and excretion of the drug; and an integrated summary of the drug's toxicological effects including results of acute, subacute, chronic, and reproductive toxicity studies./ The results of toxicology studies that support the safety of the proposed clinical study should include full tabulations of data for a detailed review by FDA./ If the product has been studied previously in humans, including foreign investigations, sponsors must provide detailed information about such studies that is relevant to the product's safety or its effectiveness for the proposed investigational use(s)./

FDA also requires that the sponsor secure approval of the clinical trial protocol by an Institutional Review Board (IRB)./ FDA regulations specify the criteria with which proposed research is to be judged by the IRB. These include: minimization of risk to the subjects, reasonable risks in relation to anticipated benefits, equitable selection of subjects, assurance of informed consent, adequate provisions for monitoring data, provisions for protecting patient privacy, and assurances that decisions to participate in research will not be coerced./

Safety Reports. During a clinical study of an investigational drug conducted under an IND, the sponsor must notify FDA and all participating investigators in a written safety report of: (1) any adverse experience associated with the use of the drug / that is both serious / and unexpected, / and (2) any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity./ The safety report must be made no later than fifteen calendar days after the sponsor's initial receipt of the information/ unless the event was fatal or life threatening, in which case a telephone or facsimile report is required within seven calendar days./

Annual reports. IND sponsors must submit an annual report for each IND. The report must include the status and progress of each ongoing study governed by that IND, as well as a general summary of information obtained during all associated clinical and nonclinical investigations in the preceding year./ The annual report must include a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system; a summary of all IND safety reports submitted during the previous year; a list of subjects who died during participation in the investigation (and the cause of death); a list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be related to the product; and a summary of significant foreign marketing developments such as withdrawal or suspension from marketing in any country./ FDA has not articulated a reasoned basis for its decision to publicly disseminate much of this information in order to protect patients enrolled in such studies, or for that matter, to protect the general public. Nor has FDA considered the negative consequences that such a disclaimer policy will have on these emerging industries.

As evidenced by the above review of FDA's regulatory requirements, the use of investigational products is subject to substantial agency oversight. Clinical trials involving gene therapy and xenotransplantation

products are carefully evaluated and monitored by FDA to assure the utmost safety relative to the potential benefit offered by the therapeutic agent.

IV. FDA's Proposal

A. The Elements of FDA's Proposal

FDA's Proposal would require the public disclosure of the existence as well as the substance of all INDs involving gene therapy and xenotransplantation products. Such information, traditionally recognized by FDA as confidential commercial and trade secret information for drugs and biologics, has never previously been made public by FDA during the investigational stage of a product's development. The Proposed Rule specifies that companies would be required to submit a redacted version of their IND information for use by the agency when responding to FOIA requests. The FDA requires the submission of a redacted version so as to assure a timely public release of the information. By FDA's own estimate the information that would be made public under the Proposed Rule would include the "vast majority" of information submitted in the initial IND, any amendments thereto, all annual reports, and all serious adverse event reports. *See* 66 Fed. Reg. at 4693. The rule also implicitly requires sponsors who opt not to publicly acknowledge the existence of their IND to waive the right to keep their research confidential. All other types of INDs and pending marketing applications are and always have been kept strictly confidential by FDA. *See* 21 CFR §§ 312.130(a); 314.430(b) and (c).

FDA contends that this radical departure from the agency's historical policy is needed because ". . . these areas of clinical research have the potential for unique public health risks and modification of the human genome." Therefore the agency has tentatively concluded that information heretofore not released prior to approval, should be released so that there can be ". . . an opportunity for public education on, and discussion and consideration of, public health and safety issues." 66 Fed. Reg. at 4688. The information FDA intends to disseminate consists of the following:

Information for public disclosure. FDA will make available for public disclosure the following types of data and information related to an IND concerning human gene therapy or xenotransplantation. Names and other personal identifiers of patients and, except as specifically provided in this section, names and personal identifiers of any third party, such as physicians or hospitals, will not be made available for public disclosure.

- Product and patient safety data and related information.
  - results of animal and in vitro studies and tests that demonstrate the safety and/or feasibility of the proposed procedures including:
    - analysis of gene transfer
    - analysis of expression
    - analysis of persistence
    - analysis of vector biodistribution
    - evidence for immune response/anergy
    - evidence for biological activity
  - results of product safety testing including:
    - testing for known xenogeneic and human infectious agents and replication competent virus
    - qualification of source herd
    - qualification of individual source animal
    - qualification of source organ/tissue/cells for xenotransplantation in humans
  - results of clinical studies and tests that demonstrate the safety and/or feasibility of the proposed procedures including:
    - analysis of gene transfer

        - analysis of expression
        - analysis of persistence
        - analysis of vector biodistribution
        - evidence for immune response/anergy
        - evidence for biological activity
    - information on monitoring or prevention of potential health risks to the recipient, close contacts, and health care workers, such as:
        - patient monitoring for replication competent retrovirus and viral shedding
        - measures taken to prevent transmission of infectious disease
- The name and address of the sponsor.
- The clinical indications to be studied.
- A protocol for each planned study, to include:
    - scientific abstract and a nontechnical abstract
    - statement of the objectives, purpose, and rationale of the study
    - name and address of each investigator
    - name and address of the official contacts of each local review body as appropriate (Institutional Review Board, Institutional Biosafety Committee) and the dated copies of each committee's approval of the study
    - criteria for patient selection and exclusion
    - estimate of the number of patients to be studied
    - description of the treatment that will be administered to patients
    - description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the safety and effects of the drug in human subjects and to minimize risk
- Written informed consent form(s).
- Identification of the biological product(s) including:
    - a description of product features that may affect patient safety
    - vector name and type
    - gene insert
    - regulatory elements and their source
    - intended target cells
    - description of the delivery system
- A general description of the method of production including:
    - source of cells, tissues, or organ(s)
    - method used to prepare the vector containing cells
    - method used to procure and prepare cells, tissues, or organs for xenotransplantation
    - purity of cells
    - adventitious agent testing
    - ancillary products used during production
    - herd colony and individual source animal health maintenance and surveillance records
    - biological specimens to be archived from source animals
- IND safety reports and other similar data and information.
- Information submitted in the annual report to include, as applicable:
    - assessment of evidence of gene transfer
    - assessment of evidence of gene expression in target cells
    - assessment of evidence of biological activity
    - assessment of evidence of immune response
    - status of autopsy request and evidence of gene transfer and gonadal distribution upon autopsy
    - results from assessment for evidence of infection by agents associated with the product
    - adverse experiences, and

- a list of subjects who died during participation in the investigation, with the cause of death for each subject
- The regulatory status of the IND:
  - *e.g.*, on hold, in effect, inactive, or withdrawn
    - the dates of these actions, and
    - the reasons for these actions
- Other relevant data and information that the Director, CBER, determines are necessary for the appropriate consideration of the public health and scientific issues, including relevant ethical issues, raised by human gene therapy or xenotransplantation.

Suffice to say the routine disclosure of such a broad array of information is unprecedented.

B. **FDA's Legal Bases for the Proposed Rule**

1. **The information required to be disclosed is no longer confidential commercial information under FOIA.**

   The principal legal basis for the Proposed Rule is FDA's assertion that the types of information that companies would be required to disclose *is no longer considered confidential commercial information* because it is already routinely available in a number of public outlets. 66 Fed. Reg. at 4693. As evidence of prior disclosure, FDA points to information made available to the RAC at NIH; at FDA/NIH workshops on xenotransplantation; in SEC filings; and through industry-sponsored websites and similar materials. As described in detail below, however, when information currently in the public domain is compared to the categories of information described in FDA's Proposal, it is clear that the Proposed Rule would encompass both trade secret and confidential commercial information.

2. **Even if the information required to be disclosed is confidential, FDA has the legal authority to authorize its release to the public.**

   Alternatively, FDA asserts that even if the information required to be disclosed under the Proposed Rule is confidential, by issuing regulations that mandate disclosure, the release of such information by FDA will be "authorized by law" as provided under the Trade Secrets Act. The Trade Secrets Act imposes criminal sanctions on government employees who disclose, in any way that is "not authorized by law," trade secret or other confidential information submitted to the government. In its Proposed Rule, FDA concludes that agency regulations that specifically provide for the disclosure of confidential information provide the requisite legal authorization under the Trade Secrets Act.

   For purposes of establishing its authority to amend its regulations, FDA cites to section 505(i) of the FD&C Act (authority to issue regulations imposing conditions on the investigation of new drugs); section 701(a) of the FD&C Act (authority to issue regulations for the efficient enforcement of the Act); section 903(b) (the agency's "mission statement"); and section 361 of the Public Health Service Act (authority to issue regulations necessary to prevent the introduction, transmission, or spread of communicable diseases). As described below, however, FDA's reliance on its regulatory authority to override its duty to prevent unauthorized disclosure of confidential information is severely misplaced.

V. RESPONSE TO FDA'S PROPOSAL

A. Contrary to FDA assertions, the information that would be disclosed under FDA's Proposal may be confidential.

FDA asserts that "the fact that these types of information cannot be considered confidential is the principal basis for issuing this proposed rule." 66 Fed. Reg. at 4693. BIO strongly disagrees with FDA's assertion. FDA has failed to establish that all of the IND information it seeks to disclose is no longer confidential. Additionally, as a matter of public health policy it is critical that this confidential commercial information continue to be protected from disclosure.

1. The fact that there has been previous public dialogue does not justify the Proposed Rule.

Both the gene therapy industry through its NIH submissions and the xenotransplantation industry, through its more limited participation at government workshops, have disclosed to the public some information that would normally be considered confidential commercial or trade secret information. In these instances, however, public disclosure has been made at the early stages of research and development for these product categories. In contrast, the more mature pharmaceutical and biotechnology sectors, and FDA, continue to hold as confidential the identical information required to be disclosed by gene therapy and xenotransplantation products under the Proposed Rule, because of the well-recognized competitive harm that can result from such disclosure. The need for these more mature industries to maintain the confidentiality of their investigational information in the future has not been questioned. There is no reason for the government to take a different position with regard to information on gene therapy or xenotransplantation products.

FDA asserts that there are unique public health risks associated with gene therapy and xenotransplantation products that require public education and discussion. Throughout the history of therapeutic product development there have always been unique public health issues facing FDA, for example, the original development of antibiotics and the present day question of antibiotic resistance; the development of highly toxic chemotherapeutic agents and radiation-emitting products; and the concerns about viral contamination of cellular products, including contamination with HIV and hepatitis. FDA has ably addressed these issues, however, without requiring wholesale disclosure of confidential commercial information related to the products at issue.

Further, there remain serious public health risks attendant to the clinical investigation of traditional pharmaceutical and biotechnology products today.

Patients in ongoing clinical trials suffer serious adverse consequences or death (for instance, the deaths of several patients in the early 1990's in a clinical investigation of fialuridine), yet FDA is not proposing a release of confidential commercial or trade secret information for all such products. FDA, along with HHS/NIH scientists and related Advisory Committees have learned to effectively address the unique and controversial public health issues of other therapeutic products without fundamentally altering the product development process and without requiring the uniform and automatic release of confidential commercial information. There is nothing in the record that suggests the methods currently employed by FDA to handle public health and safety concerns cannot apply equally as well to the issues surrounding gene therapy and xenotransplantation products. Moreover, companies engaged in gene therapy and xenotansplantation product development have to date been, and continue to be fully committed to promoting public dialogue on specific health and safety concerns as the need arises. There is no justification for imposing a blanket rule mandating disclosure on the gene therapy and xenotransplantation industry, no evidence that without such a rule FDA will not be able to protect the public health, and no basis for the resultant competitive damage that will be inflicted on developers of these products under the Proposed Rule.

As a matter of public policy, it would appear that FDA is inappropriately penalizing the industry's public participation to date by asserting that public-spirited conduct establishes that such information now and in the future can no longer be considered confidential. If FDA takes away the traditional expectation of confidentiality for the product development process, it will have serious long-term effects on the successful development of these life-saving therapies.

2. **The release of limited information by companies does not establish that such information may no longer be confidential.**

Gene therapy companies generally have cooperated with NIH in providing a limited amount of information to NIH regarding their clinical trials. That information, which is made public, includes the protocol and informed consent as well as brief summaries of safety, efficacy and manufacturing data in response to the questions contained in Appendix M of the NIH Guidelines. FDA's Proposal could be interpreted to require substantially more information that is considered confidential commercial information and even trade secret information as defined in section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 331(j)). A

brief review of several categories of information in FDA's Proposal illustrates this concern.

The section of the proposed rule that sets forth the categories of information to be disclosed is 21 CFR § 601.52(c). It contains ten categories of information. *See supra* pages 16-19. The first category is product and patient safety data and related information. 21 CFR § 601.52(c)(1). This section identifies "results of preclinical and clinical studies that demonstrate the safety and/or feasibility of the proposed procedures." It then identifies numerous specific types of information that may be disclosed but also states that this category of publicly disclosable information is "not limited" to the enumerated categories. Test results for preclinical and clinical studies have long been considered confidential commercial information by the biotechnology and pharmaceutical industries.

Categories two, three, and four require sponsors to acknowledge the existence of their investigational products, the indication(s) they are pursuing, and the protocols that outline how they expect to pursue each indication. Individual sponsors may, in the past, have chosen to share such information through the NIH process and other public outlets. It is, however, still material that has long been considered confidential and protectable by the pharmaceutical and biotechnology industries.

The sixth category of information to be disclosed deals with the identification of the product and general descriptions of the manufacturing methods. 21 CFR § 601.52(c)(6). The Proposed Rule describes a number of specific categories of information that must be disclosed including several that are trade secret information such as "method used to prepare the vector containing cells," "method used to procure and prepare cells," and "ancillary products used during production." The eighth category of information includes information to be submitted in an annual report. 21 CFR § 601.52(c)(8). This information would include updates on the safety and efficacy of the product similar to what is now submitted to FDA in an IND annual report. 21 CFR § 312.33. These summaries of safety and effectiveness are carefully protected by the rest of the pharmaceutical industry as confidential commercial information. (*See also*, footnote 36.) Lastly, the tenth category of information is anything that FDA in the future determines should be disclosed to effectuate the public consideration of these issues. 21 CFR § 601.52(c)(10). FDA, of course, cannot arbitrarily add information to the list of information to be disclosed that it has yet to identify as doing so would not provide industry any notice or opportunity to comment.

FDA has not established that the information provided to NIH by gene therapy companies for public disclosure is consistent with the broad and uncertain disclosure required under the Proposed Rule. Nor can FDA find such support since, as discussed directly above, the categories of information enumerated in the Proposed Rule merely suggest examples of the information that will be available for public release. For example, regarding the tenth category, FDA arbitrarily states that it will include any future information FDA needs.

BIO believes that there are substantial differences between what companies are publicly disclosing to NIH and what FDA could require to be disclosed in a properly redacted IND under the Proposed Rule. Additionally, as noted previously, there are gene therapy clinical trials that are not subject to NIH jurisdiction and for which such information is not publicly available through NIH. Moreover, given BIO's comments to NIH (*see supra* note 1) objecting to disclosure of confidential information, it is reasonable to assume that the amount of information publicly disclosed at NIH may change in the future. Consequently, FDA should not be relying on current disclosure policies in that forum for purposes of justifying its own regulatory proposal regarding future disclosures by FDA of IND information.

With regard to xenotransplantation, a limited number of companies have participated in various public meetings sponsored by FDA and/or HHS since approximately 1998. Companies have provided some limited information on the safety of their products; their protocols and their methods of manufacturing. Undoubtedly much of this information, if not voluntarily disclosed by the company, would have been considered trade secret and/or confidential commercial information and deserves to retain that status in the future. It is critical to understand that such information was provided voluntarily in the interest of fostering the precise dialogue FDA now claims needs to occur. It is also significant that most xenotransplantation companies have not participated in these public meetings. Finally, there is no continuing public release of such information to NIH or other regulatory agency. Thus, there is simply no concrete factual evidence in the record to establish that this information is no longer deemed confidential by the industry.

The limited public disclosure of confidential commercial and trade secret information in the past represents much less than the amount of information that FDA is demanding for public release over the lifetime of an IND. To require such far-ranging and damaging public disclosure based on the existing factual record would be arbitrary and capricious.

3. **The Proposed Rule would require public disclosure of IND information far beyond what is disclosed under Federal Securities laws and what is routinely contained in other company related materials.**

FDA seeks to further justify the breadth of the Proposed Rule, in part, by stating that "information related to the categories of information FDA proposes to disclose is available through publicly accessible filings to the Securities and Exchange Commission ("SEC")." FDA misunderstands the scope and focus of SEC disclosure requirements. In fact, the SEC disclosures are limited to particular material information that would be relevant to the average investor. The SEC does not require disclosure of the volume of technical and proprietary records and information that would be disclosed under the Proposed Rule. SEC requirements designed to insure that investors have a general understanding of companies in which they invest is far too fragile a string to bootstrap a vast new regulation that would significantly change the gene therapy and xenotransplantation industries.

The disclosure requirements for public companies are contained in two statutes. The disclosure requirements for companies seeking to register securities with the SEC are contained in the Securities Act of 1933/ and SEC rules promulgated thereunder, while the periodic and ongoing disclosure obligations of public companies are contained in the Securities Exchange Act of 1934/ and SEC rules promulgated thereunder. Both statutes require disclosure of certain material information. Information is material if a reasonable investor would consider the information important in making an investment decision. /

Public companies are not required to disclose all material information. Instead, companies are required to disclose information only as mandated by line-item SEC disclosure rules, most of which are contained in Regulation S-K./ The requirements of Regulation S-K pursuant to which gene therapy and xenotransplantation companies disclose their products, clinical trials, development pipelines and other information about drug development and delivery are Item 101, which requires the company to provide a description of its business, products and each segment of its business, and Item 303, which requires management to discuss and analyze the company's financial condition and results of operations. In addition, Item 601 requires the company to file as exhibits certain enumerated documents, including material contracts not made in the ordinary course of business.

Even in a Form S-1 one of the most comprehensive SEC-mandated disclosure documents gene therapy and xenotransplantation companies disclose only very limited summaries of their products and pending clinical trials. In a typical Form S-1, a company may include a two or three page summary of the company's business followed by a more detailed description spanning ten to twenty pages. The business section may have as little as one paragraph devoted to each major product and any ongoing clinical trials related to that product. The results of a phase of clinical trials, if made public, ordinarily would be summarized in one or two sentences. In addition, the company typically would include one or two risk factors, each a paragraph or two in length, related to the uncertainties of clinical trials and FDA approval. None of this investor-related information is intended to convey technical information of the type contained in an IND. In fact, the SEC's "Plain English" rules specifically prohibit companies from using "highly technical business terminology."/

Gene therapy and xenotransplantation companies are required to file as exhibits to their registration statements (and their reports on Form 10-K and Form 10-Q) copies of their material agreements, including license and marketing agreements. Companies typically do not file documents related to clinical trials as exhibits to SEC filings. In addition, companies are allowed to redact trade secrets and commercial or financial information including confidential pricing and design information, by requesting confidential treatment of the information./

Lastly, FDA cites to a series of private and public websites and generally asserts that they contain the information that they now conclude is no longer confidential. As with the SEC discussion above, the amount and depth of information contained on such sites is generally for the lay reader and/or investor. There is no factual basis in the record to support a contrary conclusion.

4. **FDA's Proposal represents a dramatic reversal of its decades old policy of maintaining the confidentiality of information associated with investigational products.**

FDA states in the preamble to the Proposed Rule that it does not consider the information required to be disclosed under the proposed regulation as proprietary because it has been made publicly available through various mechanisms and its disclosure has not impeded commercial development. 66 Fed. Reg. at 4691. Thus, with a summary wave of its hand, the agency sweeps aside over 60 years of agency precedent and industry

expectations regarding the confidentiality of information relating to products under investigation.

FDA and the courts traditionally have agreed that IND information is confidential commercial information protected from disclosure under FOIA. In the preamble to the Proposed Rule FDA admits that:

Historically, much of the data and information submitted in IND and unapproved biological product files has been considered confidential commercial information.

66 Fed. Reg. at 4693. Even with the agency's broad expansion of its disclosure policy in 1974, as mandated by FOIA, the confidentiality of information pertaining to an investigational product has been held inviolate, as reflected in FDA's current regulations:

601.50 Confidentiality of data and information in an investigational new drug notice for a biological product.

a. The existence of an IND notice for a biological product will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.
b. The availability for public disclosure of all data and information in an IND file for a biological product shall be handled in accordance with the provisions established in § 601.51.

601.51 Confidentiality of data and information in applications for biologics licenses.

(c) If the existence of a biological product file has not been publicly disclosed or acknowledged, no data or information in the biological product file is available for public disclosure.

(d)(1) If the existence of a biological product file has been publicly disclosed or acknowledged before a license has been issued, no data or information contained in the file is available for public disclosure before such license is issued, but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue.

21 CFR §§ 601.50 and 601.51. *See also* 21 CFR § 312.130 and 21 CFR § 812.38. Indeed, until now, FDA has never wavered from its treatment of information relating to an investigational product as confidential:

Drug manufacturers have always claimed trade secret status for the data generated from preclinical and clinical trials, on the theory that these data provide an important competitive advantage over those who do not have access to it. The Agency has generally agreed with this position since enactment of the Federal Food, Drug, and Cosmetic Act in 1938, by interpreting the term "method or process which as a trade secret is entitled to protection" in section 301(j) as encompassing animal and human testing data./

Suddenly, however, FDA proposes that its long-standing tradition of protecting the confidentiality of all information contained in an IND, of protecting even the fact that an IND exists, will no longer apply to gene therapy and xenotransplantation products.

Not only would FDA's Proposed Rule overturn decades of agency interpretation of law and policy, but it would also undercut a substantial body of judicial precedent upholding the confidentiality of information relating to products under investigation. In FOIA cases attempting to obtain the release of information from FDA, courts have consistently held that where competitive injury can be shown, commercial information contained in an IND is confidential and protected from disclosure under Exemption 4. For example, in *Public Citizen Health Research Group v. FDA*, 185 F.3d 898 (D.C. Cir. 1999), a FOIA request was made for the release of information contained in investigational new drug applications that had been abandoned by Schering Corporation when clinical testing revealed serious risks. 185 F.2d at 903. The D.C. Circuit, recognizing the confidential nature of information contained in four out of the five INDs at issue, upheld the treatment of IND data as confidential and remanded the case for a determination of whether any non-confidential information could be segregated and disclosed. *See also Public Citizen Health Research Group v. FDA*, 539 F.Supp. 1320, 1327 (D.D.C. 1982) (information that would disclose to competitors, free of charge, the benefits of costly research and testing held to sustain a claim of substantial competitive injury); *Public Citizen Health Research Group v. FDA*, 704 F.2d 1280, 1291 (D.C. Cir. 1983). In each of these cases, FDA defended its long-held policy of nondisclosure.

B.It would be arbitrary and capricious agency action for FDA to release this IND information pursuant to FOIA based on the erroneous factual claim that this information has been publicly disclosed and is no longer confidential.

1.Under FOIA, commercial information is confidential, and protected from disclosure by FOIA Exemption 4, if disclosure would "cause substantial harm to the competitive position of the person from whom the information was obtained."

Exemption 4 of the FOIA protects "trade secrets and commercial and financial information obtained from a person [that is] privileged or confidential." 5 U.S.C. §552(b)(4). Since 1983, FDA and the Court of Appeals for the District of Columbia have applied a narrow definition of the term trade secret for purposes of evaluating information against Exemption 4 of FOIA. *See Public Citizen Health Research Group v. FDA*, 704 F.2d 1280, 1288 (D.C. Cir. 1983). A trade secret is defined as

> a secret, commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort.

Id. Importantly, chemistry, manufacturing and control (CMC) information falls within the ambit of the trade secret definition. *See Public Citizen Health Research Group v. FDA*, 997 F. Supp. 56 n.2 (D.D.C. 1998).

In order to qualify under Exemption 4 as "commercial or financial information," the information must be (1) commercial or financial, (2) obtained from a person outside the government, and (3) privileged or confidential. *National Parks and Conservation Ass'n. v. Morton*, 498 F.2d 765 (D.C. Cir. 1974). Information is of a commercial or financial nature if it relates to business or trade. *Public Citizen Health Research Group v. FDA*, 704 F.2d 1280, 1290 (D.C. Cir. 1983). The term "person" refers to a wide range of entities, including corporations. There is no question that both of these requirements are met by the information submitted by BIO's members to FDA. The only question in this matter is whether the information qualifies as "confidential" for purposes of the FOIA.

The courts use different tests to determine whether information is within Exemption 4, depending on whether the information is voluntarily or mandatorally submitted to the government. As the Department of Justice has acknowledged in its manual on the FOIA, "submissions that are required to realize the benefits of a voluntary program are to be considered mandatory." DOJ Freedom of Information Act Guide (May 2000); *See also Critical Mass Energy Project v. NRC*, 975 F.2d 871 (D.C. Cir. 1992). FDA, the industry, and the courts have all recognized that IND submissions are to be considered mandatory for FOIA purposes. Accordingly, as recognized by the court in *Critical Mass*, the following test set forth in *National Parks* should be applied to determine whether information qualifies as confidential under FOIA Exemption 4:

> To summarize, commercial or financial information is "confidential" for purposes of the exemption if disclosure of the information is likely to have either of the following effects: (1) to impair the Government's ability to obtain necessary information in the future; or (2) to cause substantial harm to the competitive position of the person from whom the information was obtained.

National Parks, 498 F.2d at 770. FDA's Proposal contravenes the judicial standard for evaluating the confidential nature of information contained in gene therapy and xenotransplantation INDs.

In order to show the likelihood of substantial competitive harm, it is not necessary to show actual competitive harm. Instead, actual competition coupled with the likelihood of substantial competitive injury is all that need be shown. *Gulf & Western Industries, Inc. v. United States*, 615 F.2d 527 (D.C. Cir. 1980). There is no question that the accumulation of safety and efficacy data is costly and that it represents a company's best judgment of how and where to expend scarce resources. Consistent with that reality, FDA has long recognized that such data submitted as part of the new drug approval process provides a competitive advantage to the submitter:

> The Commissioner concludes that there can be no question, under present law, about the tremendous economic value of the full reports of

> safety and effectiveness data contained in an IND, NDA, INAD, or NADA. Such information costs hundreds of thousands, and in some instances, millions of dollars to obtain. Release of such information would allow a competitor to obtain approval from the FDA for marketing an identical product, at a mere fraction of the cost.

39 Fed.Reg. 44634 (1974). Courts have also concluded that competitive harm may result where disclosure of data submitted in an IND may be used by a competitor for purposes of determining the feasibility of pursuing similar avenues of research and development. *See e.g., Public Citizen Health Research Group v. FDA*, 964 F.Supp. 413, 415 (D.D.C. 1997) (suggesting that a claim of competitive harm could stem from the notion that disclosure of a protocol would provide "insight" into pre-approval test results and future marketing strategies).

2.The comments from BIO's members demonstrate the substantial competitive harm that public disclosure of this confidential commercial information would cause.

Both gene therapy and xenotransplantation are heavily (and, in some cases, almost exclusively) dependent on private investment sources to support their lengthy and complicated scientific product development process. In both areas, the diseases that are being studied are almost exclusively serious or life-threatening. There is substantial competition amongst companies within specific disease areas both to be first to bring such a product to the market and to raise the huge amounts of capital necessary to reach that goal. It has been estimated that it will take approximately 7-10 years and 350 million dollars on average to develop and obtain approval of a gene therapy or genotransplantation product. Thus there can be no question that these are highly competitive biotechnology product development categories.

For the remainder of the biotechnology industry and the entire traditional pharmaceutical industry, the kind of information that would be disclosed under FDA's Proposal is always treated as trade secret and/or confidential commercial information. That is certainly no different for these two product sectors. Disclosure of serious adverse event reports and annual reports prior to FDA approval could cause substantial competitive harm to a sponsor. For example, some experiences during a clinical trial that would be classified as "adverse events" might in fact suggest a new indication for research and development. Disclosure of such an event might have little bearing on patient safety or the public dialogue FDA hopes to promote, but could cost the company the opportunity to patent its product for the new indication in question. To give another example, the rate of adverse events can indicate the number of patients currently enrolled in clinical trials of a product. From this information, a competitor could determine the stage and the pace of a company's product development.

Similarly, the information in an annual report would be of tremendous value to a competitor in the early stages of developing a competing product. A competitor could combine dose response information, preliminary effectiveness reports, and preclinical study results (submitted to NIH before the trial commences) to design a study specifically to demonstrate the superiority of its competing drug. (Ordinarily, under the current disclosure rules, a competitor would not have enough information to tailor its investigational plan in this manner.) Dose response information could tell the competitor which dose levels work and which do not. Dose response information combined with adverse event reports might show the maximum tolerable dose. The number of patients completing the trial, and the number of patients that have dropped out, could indicate if there was a problem with the study design, protocol requirements, dose, testing, or logistics. The previous year's clinical and non-clinical investigations could give a competitor an inside view of a company's development plan and perhaps even insight as to the specific animal models being developed for preclinical work. Protocol amendments to expand patient cohorts, or the addition of preclinical studies, could tell a competitor whether a company has made process changes. In short, disclosure of the information in an adverse event report and an annual report could allow a competitor to duplicate a company's work without the same expenditure of time and money, or even allow it to avoid expensive and time-consuming research altogether. Such reports, therefore, contain precisely the kind of data that the courts have held to be within Exemption 4.

3.Release of most IND information by FDA can only be done on a case-by-case basis after an agency finding that release would not cause competitive harm.

The test set forth in *National Park* focuses on evidence of competitive harm on an individualized basis. Executive Order 12,600 recognizes the individualized nature of FOIA decisions under Exemption 4 by requiring agencies to give specific notice to individual submitters of proprietary information and to provide a reasonable period of time within which an individual submitter can object to disclosure of its information and can provide factual information to support its contention regarding confidentiality. 52 Fed. Reg. 23781 (June 23, 1987). Accordingly, FDA cannot use any limited release of information by some companies in the past to deny an individual submitter the right to demonstrate that it would suffer competitive harm in the future by release of specific information in its particular situation. Instead, pursuant to *National Park* and Executive Order 12,600, any release of information by FDA can only be done after an agency finding that release would not cause competitive harm in a particular case.

The opportunity to identify all of the grounds upon which disclosure is opposed is critical to submitters in order to maintain confidence in the agency's ability to properly protect confidential commercial information. Wrongful disclosure of information that should have been withheld under Exemption 4 of FOIA will support a "reverse FOIA" suit against FDA under the Administrative Procedure Act. *See Chrysler Corp. v. Brown*, 441 U.S. 281 (1979). Wrongful disclosure under Exemption 4 may even result in criminal liability under the Trade Secrets Act, 18 U.S.C. § 1905. *See CNA Fin. Corp. v. Donovan*, 830 F.2d 1132, 1151-52 (D.C.Cir. 1987), *cert. denied* 485 U.S. 977 (1988).

FDA seeks to justify its proposed regulation by suggesting that the type of information covered by the proposal has been customarily disclosed to the public by some members of the industry. FDA seems to be seeking to bring itself within the ruling of the D. C. Circuit in its *Critical Mass* decision. However, the *Critical Mass* decision cannot be used to support the proposed regulation. To begin with, that case is distinguishable since it applies to information provided on a voluntary basis, and thus is inapplicable to information, such as the IND submissions in question here, which have uniformly been treated by FDA, the industry and the courts as mandatory submissions. Moreover, *Critical Mass* merely provides that Exemption 4 protects from disclosure where it is shown that the information in question "would customarily not be released to the public by the person from whom it was obtained." 975 F.2d at 878-879. Nothing in *Critical Mass* requires disclosure in a way that precludes a company from submitting factual evidence establishing that, regardless of what might have been done in the past with some information, the company would suffer substantial competitive harm in the future if the particular information in question was disclosed.

4.Given the risk of competitive harm, it would be arbitrary and capricious for FDA to release this IND information.

The Administrative Procedure Act requires that FDA act in a fashion that is not arbitrary or capricious, an abuse of its discretion, or otherwise not in accordance with law. *See Zeneca, Inc., v. Shalala*, 213 F.3d 161 (4th Cir. 2000); *Arent v. Shalala*, 70 F.3d 610 (D.C. Cir. 1995). In light of the evidence in the record as to the competitive harm that could be caused by the release of the information called for in FDA's proposed regulation, it would be arbitrary and capricious for FDA to adopt this proposed regulation. It would be arbitrary and capricious for the agency to otherwise seek to coerce an IND applicant into "voluntarily" providing information for public disclosure as a condition for proceeding with its IND clinical trials. Instead, in the event that FDA seeks disclosure of any IND information that has historically been treated as confidential, FDA can do so only on a case-by-case basis after an agency finding that release of the information would not cause competitive harm in that particular situation. Further, it would be arbitrary and capricious for FDA to finalize this extraordinarily broad rule based upon the extremely limited factual record that exists. *See Motor Vehicle Manufacturer's Ass'n. v. State Farm Mutual Automobile Insurance Co.*, 463 U.S. 29(1983); *Teva v. FDA*, __ F.3d __, 2000 WL 1838303 (D.C. Cir. November 15, 2000). The last category of information cited in FDA's proposed regulation (21 CFR § 601.52(c)(10)), designed to act as a catchall for whatever the agency decides to disclose in the future, is especially indicative of the arbitrariness of the Proposed Rule.

C. **FDA lacks the authority to require the release of confidential information submitted under an IND.**

FDA also argues that it can support the rule on a separate and independent basis. According to the agency, even if all of the material at issue in the proposed rule is confidential commercial information, FDA can nevertheless authorize full public dissemination by issuing an appropriate disclosure rule. We disagree with the agency's reasoning on several levels.

1. **FDA has no discretion to authorize the release of trade secret material.**

   BIO disagrees with the premise that the information at issue is, at most, confidential commercial information. As noted in section V.B.1. of our comments, the information described in section 601.52(c) of the proposed rule includes significant amounts of trade secret material.

   Section 301(j) makes it a crime for any person within FDA (or the Department, for that matter) to disclose information acquired under the new drug or investigational new drug provisions of the FD&C Act concerning "any method or process which as a trade secret is entitled to protection." 21 U.S.C. 331(j). The only exceptions permitted under section 301(j) are for the release of information in judicial proceedings or certain legislative proceedings. In all other respects, section 301(j) fully relieves FDA of any discretion to issue regulations authorizing the release of trade secret material to the public.

   For example, each of the 13 specific categories in section 601.52(c)(6) describes information that, for gene therapy and xenotransplant products, meets the definition of a trade secret under section 301(j) of the FD&C Act and 21 CFR § 20.61(a). Taken as a whole, section 601.52(c)(6) would require a sponsor to disclose its entire means and method of production from isolation of source material, to the methods used to procure, prepare and assay host cells, to the insertion of the relevant gene, to the means of delivery. Under any definition, this is core trade secret material. Moreover, for gene therapy and xenotransplantation products, the productive process and the final product are nearly inseparable; to disclose the information listed by FDA is, in no uncertain terms, to "give away the store."

   The agency's statement that it is seeking only a "general description of the method of production" (proposed section 601.52(c)(6)) cannot overcome the problem. The list of specific items to be disclosed by FDA is far from "general." Indeed, for the information to be useful, it will have to be specific. However, if it is specific, it is fully protected under section 301(j). The agency cannot have it both ways, and it certainly cannot issue a rule that would allow for the dissemination of information that is clearly within the scope of section 301(j).

2. **When Congress intends to require the release of confidential information, it provides specific exceptions for doing so in the FD&C Act.**

BIO disagrees with the agency's position that FDA may use general rulemaking authority to create specific exemptions that require the disclosure of confidential commercial information. Congress provided the agency with a broad grant of authority under section 701(a) to issue rules as needed to support the efficient enforcement of the Act. Congress also authorized the agency to issue rules under section 505(i) to support the safe study of investigational new drugs. Congress did not, however, authorize FDA to issue regulations authorizing the disclosure of information that is otherwise subject to protection under an array of federal statutes. Indeed, where Congress intended for the agency to release confidential information, Congress included specific statutory exceptions within the FD&C Act.

In this way, the proposed rule stands in conflict with a fundamental principle of statutory construction: When exceptions to a general rule are specified by statute, other exceptions are not to be implied or presumed (*expressio unius est exclusio alterius*). Section 505(l) of the FD&C Act is one such specific exception authorized by Congress. Section 505(l) provides an exception to the general rule against non-disclosure of confidential information, by allowing for the release of safety and effectiveness data submitted in a new drug application when certain specific conditions have been met. *See Public Citizen Health Research Group v. FDA*, 185 F.3d 898, 902 (D.C. Cir. 1999) ("[W]hen the Congress enacted section 355(l) [505(l)] it did not mandate disclosure of information in an IND.")

In 1997, Congress added section 505B to the Act, to allow for the disclosure of confidential information about the existence of and status of postmarketing studies. As FDA recently explained, "[s]ection 506B provides FDA with statutory authority to disclose data and information, including certain information that may be considered to constitute confidential commercial information." *FDA Draft Guidance for Industry: Reports on the State of Postmarketing Studies Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (April 2001). Without such specific grants of authority, the agency cannot require the disclosure of information that is otherwise statutorily exempt under Exemption 4 to the FOIA.

3. **FDA has not been delegated the authority to issue the Proposed Rule.**

BIO disagrees with the agency's conclusion that it has specifically been delegated the authority to issue a general rule requiring the release of confidential commercial information submitted under an IND. As the agency is aware, Exemption 4 protects both trade secrets and confidential commercial information, and it protects the interests of the government *as well as the interests of the submitter.* FDA as a general matter, is precluded under the TSA, from releasing any information that falls within the scope of Exemption 4 of the FOIA, including confidential commercial information. *See McDonnell Douglas Corp. v. NASA*, 180 F.3d 303, 305 (D.C. Cir. 1999).

More specifically, the Trade Secrets Act (the "TSA") prohibits (by criminal prosecution, imprisonment, and loss of employment) the release of trade secret and commercial information, unless "authorized by law." 18 U.S.C.

1905. The TSA acts as a general prohibition or restraint on the freedom of government employees to disseminate confidential information to third parties. *See generally CNA Fin. Corp. v. Donovan*, 830 F.2d 1132, 1149 (D.C. Cir. 1987), *cert. denied* 485 U.S. 977 (1988). The scope of the protection required by the TSA is considered to be coextensive with the scope of the protection under FOIA Exemption 4. Accordingly, when a person submits to the federal government information that falls within Exemption 4, the government is precluded under the TSA from releasing that information. *McDonnell Douglas Corp.,* 180 F.3d at 305.

This general prohibition may, however, be set aside if the disclosure at issue has been "authorized by law" within the meaning of the TSA. FDA claims in the proposed rule that it has ample statutory authority to authorize the disclosure of information otherwise covered by the TSA. As discussed above, the agency in fact has no discretion to authorize the release of trade secret material described in section 301(j) of the FD&C Act. We also believe, for the reasons discussed below, that neither the FD&C Act nor the PHS Act authorizes the agency to issue regulations that would allow, as a general matter, confidential commercial information developed under an active IND to be released to the public. Although the FD&C Act includes several provisions that specifically authorize the release of commercial information, Congress has not provided FDA with general authority to issue rules requiring the release of such information.

The authority to issue regulations requiring the disclosure of confidential information must be based on a specific grant from Congress, and is subject to any limitations that Congress may have imposed. *See Chrysler v. Brown*, 441 U.S. 281, 308 (1979) (the central issue is whether the statutory grant of authority cited by the agency contemplated the regulations providing for the release of the information). In *Chrysler*, the Court analyzed whether the Department of Labor ("DOL") had the authority to require the disclosure of certain confidential employment information and, in doing so, stated the following standard:

The pertinent inquiry is whether under any of the arguable statutory grants of authority the [DOL] disclosure regulation . . . are reasonable within the contemplation of that grant of authority. *We think it is clear that when it enacted these statutes, Congress was not concerned with public disclosure of trade secrets or confidential business information, and, unless we were to hold that any federal statute that implies some authority to collect information must grant legislative authority to disclose that information to the public, it is simply not possible to find in these statutes a delegation of the disclosure authority asserted by the [DOL] here.* [emphasis added]

Id. at 306. With that standard in mind, we believe FDA has failed to identify a source of authority to support each release of confidential information required under the proposed rule.

a.Section 505(i) does not authorize the disclosure of confidential information

The primary source of authority relied upon by FDA is section 505(i) of the FD&C Act. Under section 505(i), the agency is authorized to issue

regulations exempting drugs intended solely for investigational use by qualified experts from the new drug approval requirements. Section 505(i) outlines the types of conditions under which Congress believed such an exemption should be granted. These include an adequate showing that the drug is safe for clinical testing and adequate procedures to ensure that patients are informed of and consent to the risks associated with the investigation. Section 505(i) also contemplates the collection of data and the submission of that information to the agency on a periodic basis. *See* section 505(i)(1)(C).

There is, however, nothing in the plain language of section 505(i) indicating that it represents a substantive grant of legislative power to promulgate rules authorizing the release of trade secrets or confidential business information. *See Chrysler*, 441 U.S. at 310. Nor can the statement in section 505(i) that FDA may consider "other conditions" relating to "protection of the public health" be taken as authorizing the public release of data collected under section 505(i). The agency reads this provision as if it were a "blank check." In fact, such an open-ended provision must always be limited by context and, in fairness, there is nothing in the surrounding language to suggest that Congress had in mind the types of disclosures found in the proposed rule. /

Recognizing the limits of the plain language of section 505(i), the agency offers a reference to legislative history. According to FDA, section 505(i) was added in 1962 as part of a larger set of amendments to the FD&C Act. One overall purpose of the larger set of amendments was, as FDA states, to make information on drugs more available to physicians and the general public. Although the agency never completes the thought, the suggestion is that the legislative history thereby supports the idea that FDA was given authority in section 505(i) to authorize the release of confidential information.

Putting aside the thin logic, the agency's factual premise is simply incorrect. The "legislative history" cited by the agency not only says nothing about the release of confidential information but, more important (and as the agency should know), it is a reference to improving the labeling of drug products and to imposing requirements on manufacturers to disseminate package insert information. / It has nothing at all to do with the release of otherwise confidential information.

In short, neither the plain language of section 505(i), nor the one piece of history cited by FDA, suggests in any way that section 505(i) was intended to authorize regulations limiting the scope of the TSA. *See Chrysler*, 441 U.S. at 312.

b.Sections 701(a) and 903(b) do not authorize the disclosure of confidential information.

Other than a reference to FDA's general authority to issue rules as needed to enforce the FD&C Act (see section 701(a)), the only other provision under the FD&C Act that FDA cites as source of authority for requiring the release of confidential business information is section 903(b), which sets forth the agency's "Mission Statement." There is nothing on the face of this provision that even remotely suggests that Congress intended for it to be used to authorize the public dissemination

of confidential business information. It is a general statement of goals and aspirations, not an independent source of legal authority for the agency.

Based on the agency's logic that a general statement of the agency's "public health" mission authorizes FDA to issue a rule as detailed and specific as this one there would be no limit to FDA's authority. *See American Pharmaceutical Association v. Mathews*, 530 F.2d 1054 (D.C. Cir. 1976). Whatever authority FDA believes was delegated to the agency under section 903(b), it does not include the authority necessary to authorize regulations overriding the scope of the TSA.

Absent a specific substantive grant of authority, FDA's reference to section 701(a) adds no additional authority. The fact that FDA's rulemaking authority has over the years been "broadly construed" (66 Fed. Reg. at 4694) simply is not enough. FDA indeed has broad authority to issue regulations related to the public health purposes of the FD&C Act, provided it can be shown that the regulations further congressional objectives memorialized elsewhere in the statute. The agency has identified only two possible sources of authority on which to base a rule under section 701(a), neither of which contemplates congressional intent to allow an exception to federal nondisclosure laws.

c.FDA cannot support the proposed rule under section 361 of the Public Health Service Act

Finally, the agency argues that it may authorize the disclosure of confidential business information under section 361 of the Public Health Service Act (the "PHS Act"). Section 361 authorizes the Surgeon General to issue regulations "*necessary* to prevent the introduction, transmission, or spread of communicable diseases . . . ." 21 USC 264(a) (emphasis added). When read in context, along with the other sources of authority delegated by Congress to the Surgeon General, there is again no statutory language to suggest that Congress intended for this provision to be used to authorize the general release of IND information otherwise protected by the TSA.

Moreover, the agency's reference to section 361 of the PHS Act highlights a critical problem with the agency's overall approach. As noted, section 361 authorizes only those regulations determined to be "necessary" to prevent the spread of communicable disease. FDA, however, has failed to show the necessary and essential link between the risk it is seeking to address under section 361 (the spread of communicable disease through the study of gene therapy and xenotransplant products) and the proposed solution (the public dissemination of confidential commercial information developed under all gene therapy and xenotransplant INDs). *See generally Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

According to the agency, "The public availability of information this proposed rule envisions will permit public attention to any emerging risks associated with these experimental techniques, early detection and definition of which will permit the agency and sponsors to take steps to prevent or minimize the introduction of communicable diseases." 66 Fed. Reg. at 4695. Whatever may be the "plain language" meaning behind

this sentence, it certainly does not establish a necessary link between the problem and the solution.

FDA has a long history of protecting the type of information described in the proposed rule. See section V.A.4. above. The agency is now taking the position that the public interest, in this instance, requires disclosure of otherwise protected information. Missing, however, from the agency's analysis is a thorough explanation as to why such an unprecedented release of confidential IND information is required and necessary in this instance. For example, there is no indication that the agency considered whether alternative approaches would have been equally effective. There is no explanation why only an across-the-board release of confidential IND information, at the time of submission, is needed to "permit public attention to any emerging risks," help with "early detection," and allow FDA and sponsors to "take steps to prevent or minimize the introduction of communicable diseases."

Before requiring such an exceptional, blanket release of confidential information, the agency must consider reasonable alternatives and show why they would not work. To do otherwise would be arbitrary, capricious, and not in accordance with law. *See, e.g., Qwest Communication International Inc. v. FCC*, 229 F.3d 1172, 1183-84 (D.C. Cir. 2000).

4. **The Proposed Rule fails to take into account, and is inconsistent with, Executive Order 12600.**

Executive Order 12600, issued June 23, 1987, requires federal agencies to establish pre-disclosure notification procedures before releasing confidential commercial information. *See* 59 Fed. Reg. 531, 532 (Jan. 5, 1994). In 1994, FDA memorialized its compliance with the terms of the Executive Order by amending its regulations under 21 CFR part 20, establishing a specific process for the submission and designation of confidential information, and for the resolution of disputes regarding the disclosure of such information. *Id.* The Proposed Rule failed to consider the Executive Order in several respects, all of which render the Proposal defective.

The Executive Order provides that notification requirements contemplated by the Order need not be followed if, among other things, the disclosure of confidential information is being required by an agency rule. In that case, however, the rule must specify only "narrow classes of records" and must provide "in exceptional circumstances for notice when the submitter provides written justification, at the time the information is submitted or a reasonable time thereafter, that disclosure of the information could reasonably be expected to cause substantial harm." E.O. 12600, sec. 8(d).

Here, the Proposed Rule is far from narrowly drawn, as required by the Executive order. On its face, the proposal is sweeping as to the type of information that would be released, as well as the products that would be impacted. It describes ten categories of information that reach into every facet of every IND for every gene therapy and xenotansplantation product. For example, according to the preamble, proposed section 601.52(c)(1) is similar to existing provisions that require the disclosure of *all* safety and effectiveness data following product approval, except that

the proposal "*would extend this throughout the entire product development process* for a product related to human gene therapy or xenotransplantation." 66 Fed. Reg. at 4696. Similarly, all indications under study, and all protocols for all products in this class, must be disclosed, as must the manufacturing methods (including 13 subcategories of information) for all such products. *See* sections 601.52(c)(3), (4), and (6). All IND safety reports would become public under the rule. Finally, the rule includes an open-ended "other information" category that is patently inconsistent with the Order.

A "narrow" rule would have sought to disclose only the most essential information, for only those products that raised a specific issue. And, a "narrow" rule would have been calibrated specifically to require only those disclosure necessary to address a well-defined, specific problem.

Second, the rule makes no provision for the type of procedure contemplated under section 8(d)(3) of the Executive Order. Even if FDA has the authority to require the release of the confidential information at issue in this rule (and, as discussed above, we do not believe that it does), it still must allow sponsors access to the same procedures applicable to all other persons who submit information to FDA and the rest of the Federal government. For example, under the proposed rule, sponsors must decide upon submission of the IND whether they will seek to protect certain information, and must do so under the threat of having their study placed immediately on clinical hold (*see* discussion, below). Opportunity for *de novo* review of the agency's disclosure decisions, on a case-by-case basis, will effectively be lost by those sponsors who are under pressure to move forward with their studies. Moreover, sponsors must "declare, under penalty of perjury" (*see* proposed section 601.53(e)) that they have not redacted information that FDA now believes it is authorized to disclose.

Such requirements, not to mention the absence of a well-structured pre-disclosure notification process. are wholly at odds with what is contemplated in the Executive Order. The agency, however, failed at all to incorporate the Order into its thinking.

D. **Public disclosure of IND information would violate the takings clause of the United States Constitution**

BIO objects to the public dissemination of IND information as proposed by FDA as a "taking" of property for public use without just compensation, in violation of the Fifth Amendment to the United States Constitution./

It is well established that trade secrets and confidential commercial information are "property" protected by the Fifth Amendment to the United States Constitution. *Ruckelshaus* v. *Monsanto*, 467 U.S. 986, 1003-1004 (1984). Consistent with that view, the Ninth Circuit has recognized that state protected property rights may exist in association with such intangible property as governmental privileges granted to private parties. *See G.S. Rasmussen & Assoc. v. Kalitta Flying Service*, 958 F.2d 896 (9th Cir. 1992), *cert. denied* 508 U.S. 896 (1993) (the right to rely on engineering and test data submitted to demonstrate the safety and airworthiness of particular aircraft modifications under requirements

of the Federal Aviation Act and the Code of Federal Regulations created a property interest under California law for the engineer who submitted the data); *see also Miles v. Scripps Clinic and Research Foundation*, 810 F.Supp. 1091 (S.D. Cal. 1993) (the intangible right to commercialization of a genetically engineered cell line existed as a state property right). Generally, with respect to such intangible property interests, "the right to exclude others is central to the very definition of the property interest." *Monsanto*, 467 U.S. at 1011. *See also id.* at 1002 ("Because of the intangible nature of a trade secret, the extent of the property right therein is defined by the extent to which the owner of the secret protects his interest from disclosure to others".). In short, the essence of ownership of a trade secret or confidential commercial information is the right to exclude others. Once secrecy has been lost, the property has been irrevocably destroyed. *Id.* at 1011-1012.

Government action constitutes a *per se* taking if it deprives the property owner of all economically beneficial use of his property, or if it constitutes an appropriation of one or more of the property owner's fundamental ownership rights in the property (including the right to exclude others from making use of the property)./ Disclosure of trade secrets and confidential commercial information compiled during the testing of an investigational new drug or biologic would do both. By disclosing information that would allow a company's competitor to duplicate its research without the same expenditure of time and money or to avoid that research altogether, FDA would strip the company of its ability to use that information profitably in a commercial setting.

At least one court has recognized the application of constitutional takings principles in the context of FDA's potential use of data. In *TRI-BIO Laboratories v. U.S.*, 836 F.2d 135 (3d Cir. 1987), a pharmaceutical manufacturer filed a generic animal drug application, incorporating in its application the research and testing data submitted by another manufacturer who had earlier obtained approval to market the predecessor brand name drug. As the court explained, FDA took the position that it could not consider the previously filed material in reviewing the generic drug application because the pioneer drug manufacturer's "proprietary interest may not be appropriated by the government without just compensation." *Id.* at 139. In reaching that decision, the court relied on the following regulatory provision: "Any reference to information furnished by a person other than the applicant may not be considered unless its use is authorized in a written statement signed by the person who submitted it." 21 CFR § 514.1(a). Thus, the court concluded, the pioneer manufacturer had a reasonable investment-backed expectation that FDA would refrain from nonconsensual use of its research material.

Even if public disclosure of information contained in an IND were not a *per se* taking, it would be a compensable "regulatory taking." Although there is no precise formula for determining when a regulatory taking has occurred, the Supreme Court examines "the character of the governmental action, its economic impact, and its interference with reasonable investment-backed expectations."/ BIO members have invested millions of dollars in the research and development of gene therapy products. Disclosure of the trade secrets and confidential commercial information contained in company INDs would have a

devastating economic impact on the sponsors of such products by compromising their future revenue and thus their ability to recoup their investments in research and development. These investments were made with the understanding and expectation that FDA would continue to comply with the federal Trade Secrets Act and would continue to withhold from public disclosure data and information within Exemption 4 of FOIA. In short, BIO members have – and continue to have – reasonable investment-backed expectations in the continued legal protection of their trade secrets and commercial information. The reasonableness of these expectations is underscored by the Department of Justice's position that the Trade Secrets Act extends to everything within Exemption 4 of the FOI Act, the Court cases confirming that safety, efficacy and other pre-approval data fall within Exemption 4, and FDA's long-held position of protecting such information from disclosure.

E. **BIO opposes expansion of the Proposed Rule.**

1. **Expansion to cover other products is unjustified as a matter of fact and law.**

FDA has requested comment on whether additional products, including but not limited to, plasmid DNA vaccines, genetically modified vial vector vaccines and replication competent viruses, should be included in this rule. BIO strongly opposes this rule generally and its expansion to include other products. FDA has made no factual record to support the release of this information, nor has it established a compelling policy rationale for such action. For FDA to add additional product categories to this rule would be arbitrary and capricious.

2. **Application of the Proposed Rule to a BLA is unjustified as a matter of fact and law.**

FDA has requested comment on whether the Proposed Rule should be expanded to apply to the same information as it exists in a Biological License Application ("BLA") at the time it is submitted. This would be yet another fundamental change in the way gene therapy and xenotransplantation products would be developed and approved. FDA is recklessly proposing a dramatic expansion in its policy on the release of information without any of the careful consideration such a proposal deserves. The agency in two brief sentences suggests the advantage (continuation of the availability of information) and the disadvantage (the amount of information that would be required to be submitted) to support the contemplated expansion.
BIO strongly opposes application of the Proposed Rule to BLA records. Its impact would be enormous on innovation; capital investment; and the successful development of these products. To pursue this proposal would be arbitrary and capricious.

F. **Enforcement of FDA's Proposal through the clinical hold mechanism is wholly inappropriate as a matter of law and policy.**

The Proposed Rule provides that sponsors may have their studies placed on clinical hold if they fail to provide the required information for public disclosure or if the information provided is improperly redacted. *See, e.g.*, 66 Fed. Reg. 4697. Utilizing this mechanism coerces companies to surrender their rights to maintain the confidentiality of commercial and trade secret information due to the enormous pressure they face to start and maintain clinical trials. It also ignores the notice procedures contemplated by Executive Order 12600 (June 23, 1987) and the agency's own regulations (*see* 21 CFR 20.61) for designating trade secret and confidential commercial information, and for resolving subsequent disclosure issues.

The FD&C Act grants the Secretary authority to place an investigation on clinical hold if "the drug involved represents an unreasonable risk to the safety of the [study subjects]" or "for such other reasons as the Secretary may by regulation establish." FD&C Act § 505(i)(3)(A)-(B); 21 U.S.C.A. § 355(i)(3)(A)-(B). This statutory provision was added to the FD&C Act as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Pub. L. No. 105-115 § 117.

Prior to FDAMA, FDA imposed clinical holds on studies in accordance with regulations governing investigational drug and biologics studies. 21 CFR § 312.42. The circumstances under which FDA could impose clinical holds, however, were related to protecting patient safety. The regulations limited clinical holds to situations involving "an unreasonable and significant risk of illness or injury," unqualified investigators, misleading, erroneous, or materially incomplete investigators' brochures, an IND that was insufficient to assess risk to subjects, or a when a phase 2 or 3 study that was "clearly deficient in design to meet its stated objectives." 21 CFR § 312.42(b)(1)-(2)(2000). Imposing clinical holds for "clearly deficient studies" served an underlying safety purpose which, as described by FDA, was to "preclude exposure of human subject to risks in an investigation that FDA concludes would ultimately have no scientific or regulatory value." 52 Fed. Reg. 8798, 8821 (1987).

The regulations also permitted clinical holds of treatment INDs, treatment protocols, and non adequate and well controlled studies for reasons, among other, such as when they were deficient or interfering with enrollment in studies designed to be adequate and well controlled. FDA also was permitted under the regulations to place studies on clinical hold conducted with informed consent waivers failing to meet certain criteria. *Id.*

The early drafts of FDAMA limited FDA's clinical hold authority to promoting subject safety. The clinical hold authority only included situations when the "Secretary determines that such action is necessary for the protection of human subjects." S. Rep. No. 104-284, at 110 (1996). Indeed, the Senate Committee on Labor and Human Resources recognized that "the Secretary may well have concerns about the design of research protocols or other aspects of the investigation which do not put human subjects at risk. This legislation does not prevent the Secretary from communicating these concerns to investigators and sponsor on changes to address such concerns." *Id.* at 25. Thus, even though Congress realized there would be other times when FDA would need to exert control over study sponsors, it did not extend the clinical hold authority to cover them.

While there is broad authority given to the Secretary to define

circumstances under which a clinical hold is appropriate, the original intent of protecting patient safety remains the underlying thrust of the FD&C Act clinical hold provision. In fact, FDA ties patient safety to the imposition of a clinical hold for failing to provide a public version or properly redacted copy of IND submissions. FDA's justifies the extreme measure of a clinical hold by stating that "it is important for proposed and ongoing human gene therapy and xenotransplantation investigations to be the subject of public education, discussion, and consideration in order for all relevant issues, including *safety*, to be explored." 66 Fed. Reg. at 4694 (emphasis added).

BIO agrees with FDA that the reason for a clinical hold primarily should be based on protecting the safety of study subjects. The proposed regulation, however, fails to provide a factual basis for why disclosure of commercial information provides such subject protection. The agency's rationale for imposing a clinical hold on sponsors is a general conclusion that:

due to the unique nature of human gene therapy and xenotransplantation, public participation in the consideration of proposed and ongoing clinical studies of such therapies is crucial. In order for such public education, discussion, and consideration to take place and be meaningful, FDA must be able to make all relevant and publicly disclosable data and information available to the public as soon as practicable.

66 Fed. Reg. 4698.

The preamble to the proposed rule, however, fails to establish any factual basis for its premise that disclosure of commercially damaging information is necessary for the protection of gene therapy and xenotransplantation research subjects nor why it must occur as soon as practicable. It is not clear how the public education, discussion and consideration of gene therapy and xenotransplantation is any more necessary to protect such research subjects than it is for the investigation of other types of products. Even if one assumes that such activities are necessary for gene transfer and xenotransplantation, FDA never explains why the commercially harmful disclosure of information regarding the feasibility of the proposed therapy/procedure or the methods of production, for example, contribute to the public's education or discussion regarding the safety of the subjects. Nor does the preamble address why the particular informed consent signed by a patient does not provide appropriate protection for patients. Further, the decision to put a clinical trial on hold is specific to that study and whether the patients in that study are at risk. A generalized conclusion that all patients in all studies are put at risk because certain information is not publicly available is an enormous policy leap that goes far beyond the appropriate use of the clinical hold mechanism.

Thus, FDA provides no specific support for its contention that commercially harmful disclosures are necessary to protect human research subjects of gene therapies or xenotransplants. Yet, the failure to provide a redacted version of such commercial information or a properly redacted version of such information, makes it impossible for a sponsor to proceed with its investigation. In other words, sponsors are universally and without exception left with the impossible choice between forfeiting information that will harm them commercially or being foreclosed from investigating their product in the United States. Without

even providing such an explanation, FDA's proposed rule of forcing every gene therapy or xenotransplant sponsor to divulge trade secret information in order to proceed with a clinical study is patently arbitrary and capricious.

VI. POLICY OBJECTIONS TO FDA'S PROPOSAL

The impact of FDA's Proposal would have extremely serious consequences for the biotechnology industry and the public that FDA has not properly considered.

A. FDA's Proposal lacks a reasoned analysis and a rational connection to the problem identified.

FDA states that gene therapy and xenotransplantation raise unique safety issues that require both public education and dialogue. Investigations of these products, ". . . call for additional mechanisms to provide the public access to clinical trial information relevant to the assessment of risks and benefits, and to informed consent." 65 Fed. Reg. at 4690. Further, FDA states that "[s]uch disclosure is necessary in order to protect the public health by informing the research community and the public of the nature and the hazards of the proposed research and by permitting comments on the merits of the proposed research." *Id.* at 4692. Unfortunately, however, FDA has not established that present industry practice of providing information necessary to allow public dialogue, coupled with FDA's authority to stop clinical investigations that raise safety concerns, do not adequately address the agency's public health and safety concerns.

Both the gene therapy and xenotransplantation industries have cooperated to a significant degree in the past to allow for substantial public discussion of safety issues. Such public discussions have occurred at NIH, FDA and HHS. BIO is confident that such reasonable cooperation will continue in the future. When one couples the existing public dialogue with FDA's well documented use of its regulatory authority, primarily the clinical hold, FDA's Proposal fails to justify how mandating the sweeping disclosure of confidential commercial and trade secret information will further the agency's goals and whether those goals are reasonably related to FDA's statutory authority. In addition, as discussed above, FDA has already demonstrated its ability to address significant and controversial safety issues raised during the development of unique therapeutic products. FDA's Proposal provides no explanation why existing practices are not sufficient to address the concerns identified in relation to gene therapy and xenotransplantation products.

It is a well-settled principle of administrative law that an agency rule is arbitrary and capricious unless it presents a reasoned analysis between the problem the agency perceives and the solution proposed in the regulation. Further, that reasoned analysis must set forth why the agency is departing from past policies (in this matter, a departure from 60 years of precedent); and how its conclusions are derived from the facts contained in the record of the rulemaking. *See Motor Vehicle Manufacturers Association v. State Farm,* 463 U.S. 29 (1983); *Bowen v. American Hospital Association*, 477 U.S. 610 (1986). FDA's Proposal fails on all such standards and must be considered arbitrary and capricious.

B. The Proposed Rule could have a negative impact on the kind of information presented to FDA and in the manner that it is presented.

Many companies currently view FDA as a knowledgeable partner and useful sounding board during the IND process as it applies to gene therapy and xenotransplantation

products. Under the present FDA practice of protecting IND information from public disclosure, such companies are often perfectly comfortable in providing the agency with more information than is specifically required under the IND regulations. They do so in order to facilitate the unstructured exchanges of ideas that are valuable from both a regulatory and scientific viewpoint during investigation of a product. Public availability of IND documents clearly would have a chilling effect on that process. Companies would be forced to consider how public disclosure of their submissions to FDA would impact the company and evaluate every piece of information submitted to an IND accordingly. Additionally, in preparing their IND submissions, companies would have to be aware of a lay audience as well as the FDA audience to whom they currently gear the presentation of IND information. Almost inevitably, companies will have to include additional, extraneous contextual information for purposes of educating the lay audience, thereby increasing the length of IND submissions and diluting the scientific focus. Thus, the logical ramifications of FDA's Proposal may very well undercut the agency's currently unfettered access to well presented company information, without any corresponding benefit to the public health or safety.

C. The Proposed Rule is likely to increase volatility of stocks and hinder ability of research companies to raise money in capital markets.

A significant unintended and unanalyzed consequence of the Proposed Rule is likely to be a substantial increase in the volatility of stocks prices of gene therapy and xenotransplantation companies. Even information of dubious value and uncertain origin can have substantial effect on a company's stock price. / Early efficacy data from clinical trials are often unreliable and may be unduly positive or negative. / As a result of the Proposed Rule, however, all of this information would be publicized and subjected to individual interpretation by analysts who may not understand the tentative and routine nature of these results. A company's stock price could gyrate up and down as partial and perhaps contradictory interim results are released. This increased volatility in stock price also could subject gene therapy and xenotransplantation companies to class action lawsuits alleging securities fraud. According to one commentator, "[t]he required disclosure of bad news that results in a company's market valuation dropping by 15 percent or more is an immediate red flag for a potential class-action suit." /

Affected companies will have limited ability to counteract the mistaken impressions of individual analysts. Under the SEC's Regulation FD, / a company risks enforcement prosecution if it selectively responds to analyst's questions. However, a market-wide attempt by a company to correct one analyst's erroneous conclusion could backfire by further highlighting the unreliable information released pursuant to the Proposed Rule.

In addition, disclosures made in IND materials filed with FDA and released to the public would be treated under federal securities laws as announcements to the market. / Because the company is obligated to disclose any information necessary to make this publicly released information not misleading to investors, the company may be forced to begin making full public disclosure regarding clinical trials well before it would otherwise be required by the carefully crafted SEC rules. It is unlikely that FDA intended to have such sweeping effects on the capital markets and securities disclosure when it promulgated the Proposed Rule. This profound, unintended consequence could lead to the delay of product development, or in some cases the cessation of product development, due to financial constraints.

D. The cost to industry has not been adequately evaluated.

FDA has concluded that since the "vast majority" of information in an IND will not be eligible for redaction under the Proposed Rule, the cost to industry will be approximately

$843 per IND submission. That conclusion substantially underestimates the cost to individual companies. The average number of volumes representing a single IND may amount to 20 or more volumes during the course of its developmental life. To ensure proper compliance with FDA's Proposal; to avoid the draconian result of a clinical hold; ensure that trade secret and confidential commercial information are not released, represents a much greater burden than FDA estimates. As individual companies company comments make clear, FDA has substantially underestimated the administrative costs associated with compliance with the Proposed Rule. Further, should the Proposed Rule be finalized, there is no doubt that there will be a huge cost to industry in terms of release of information considered by individual companies to be confidential.

E. E.The ability of FDA to enforce the Proposed Rule fairly is highly suspect.

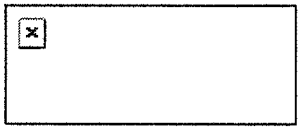
In order to police the Proposed Rule so as to ensure that all companies are complying with the final disclosure requirements in a timely, fair, and even-handed manner, will place enormous administrative burdens on FDA. For FDA to finalize the Proposed Rule, which would have such enormous consequences for the relevant portions of the biotechnology industry, and then to fail in the full and fair enforcement of the rules, would be arbitrary, capricious, and an extraordinarily poor public health policy decision.

VII.CONCLUSION

Human gene therapy and xenotransplantation products hold great promise for treating some of humanity's most dreaded diseases. Policy decisions by FDA that would discourage or delay development of these important products would be in direct opposition to the public health interest the agency has been ordained to protect. There are mechanisms available that would allow reasonable public education and discussion without seriously injuring a company's ability to raise capital and develop such products. FDA's Proposal, as a matter of fact, law and policy is defective and should be withdrawn.

Respectfully submitted,

BIOTECHNOLOGY INDUSTRY ORGANIZATION



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